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Dkt. 30436.11-US-01/SLM/KM

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Applicants: Peter S. Linsley, Jeffrey A. Ledbetter,  
Nitin K. Damle, and William Brady

#52  
D.81  
9/23/98

Serial No.: 08/219,200

Examiner: P. Gambel

Filed: March 29, 1994

Group Art Unit: 1806

For: LIGAND FOR CD28 RECEPTOR ON B CELLS AND METHODS

35 N. Arroyo Parkway, Suite 60  
Pasadena, CA 91103  
September 10, 1998

Honorable Assistant Commissioner for Patents  
Washington, D.C. 20231

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SEP 15 1998

SIR:

APPEAL BRIEF

**GROUP 1800**

Applicants hereby appeal to the Board of Patent Appeals and Interferences from the final Office Action issued December 10, 1997. A response to the Office Action was due March 10, 1998. A three month extension of time for responding to the Office Action was requested and the required fee was paid. A response to the final Office Action was due June 10, 1998. In lieu of a response, a Notice of Appeal was filed June 10, 1998 with a request for a three month extension of time with the proper fee. An Appeal Brief was due August 10, 1998. A one month extension of time for filing the appeal brief is requested. The fee under 1.17(f) of \$310.00 for Filing a brief in support of an appeal, the fee under 1.17(g) of \$270.00 for a Request for oral hearing, and the fee under 1.17(a) of \$110.00 for one month extension of time to file the Brief, for a total of \$690.00, is due. Applicants authorize the Patent and Trademark Office to charge the amount of SIX HUNDRED AND NINETY DOLLARS (\$690.00) to Deposit Account 50-0306. Accordingly, this Appeal Brief and the concurrently submitted Amendment are being timely filed.

Appeal

Linsley et al.  
U.S. Serial No. 08/219,200  
Filed: March 29, 1994  
Page 2

An oral hearing is hereby requested.

### **1. REAL PARTY IN INTEREST**

The parties named in the caption are the inventors of the claimed methods. Further, the inventors have assigned their interest in the subject application to Bristol-Myers Squibb Company.

### **2. RELATED APPEALS AND INTERFERENCES**

At the present time there are no pending appeals or interferences related to this case.

### **3. STATUS OF CLAIMS**

Claims 1-78, 95 and 96 have been canceled. Claims 79-94 are pending and have been rejected by the Examiner (pending claims are attached hereto as Exhibit 1). Claims 79 and 88 are being amended in the Supplemental Amendment concurrently filed herewith (attached for convenience as Exhibit 3). No claims have been allowed.

### **4. STATUS OF AMENDMENTS**

Applicants have submitted a Supplemental Amendment concurrently with the Appeal Brief which requires entry on the record (attached as Exhibit 3). To date, the Supplemental Amendment has not been acted on by the Examiner.

## 5. SUMMARY OF THE INVENTION

Applicants' invention involves the heretofore unknown discovery that blocking the CD28/CTLA4/B7 pathway ("the pathway") results in the inhibition of T cell responses including proliferation, caused by the interaction of T cells with B cells.

The claimed invention is directed to methods for using soluble B7 or CD28 fusion proteins to block the pathway, resulting in inhibition of T cell proliferation. The methods comprise contacting CD28 positive T cells with a soluble B7 fusion protein so as to bind the CD28 receptor on the CD28 positive T cells. This binding blocks the pathway and prevents interaction of T cells with B cells thereby resulting in inhibition of T cell proliferation. Any portion of the B7 protein which binds to the CD28 receptor on the T cells and achieves inhibition is included in the claimed methods (Table 3) (specification at page 9, lines 16-19, lines 27-30; page 10, lines 5-25; page 20, lines 34-35; page 21, lines 1-30; page 22, lines 1-32; page 23, lines 3-18; lines 33-35; page 24, lines 1-35; page 25, lines 1-23; page 26, lines 20-35; page 27, lines 1-4, lines 19-36; page 28, lines 1-10; page 37, lines 29-35; pages 38-44, pages 46-51; page 56, lines 14-35; page 57, lines 1-12; pages 59-72).

Additionally, the invention also includes methods for inhibiting the binding of B7 positive B cells to CD28 positive T cells. This is achieved by contacting B7 positive cells with a soluble CD28 fusion protein which recognizes and binds B7. This prevents the binding of the B7 positive B cells to CD28 positive T cells, and thus also inhibits T cell B cell interactions.

While the methods of the invention can be used to accomplish therapeutic goals in humans they are not limited to such a use. The invention is directed to the use of a soluble CD28 fusion protein or a soluble B7 protein, to bind B7 positive B cells or CD28 positive T cells, respectively. This binding inhibits T cell responses which are associated with the binding of the B cell and the T cell. So long as the binding is accomplished in the manner claimed, T cell responses, that rely on the binding of B and T cells, will be inhibited. This can be accomplished *in vitro* or *in vivo*.

## 6. ISSUES

### A. REJECTION OF SPECIFICATION AND CLAIMS 79-96 BASED UPON 35 U.S.C. §112, FIRST PARAGRAPH

The first issue is the Patent Office's remaining rejection of the specification and claims 79-96 under 35 U.S.C. §112, first paragraph, as allegedly not enabling any person skilled in the art to use the invention. The Patent Office asserts that "The specification does not adequately teach how to effectively treat any disease or reach any therapeutic endpoint in humans by B7Ig or CD28Ig fusion proteins. The specification does not teach how to extrapolate data obtained from the disclosed in vitro assays based upon B7 Ig or CD28 Ig or from other CD28-B7 inhibitors such as antibodies or CTLA-4 Ig to the development of effective in vivo human therapeutic methods, commensurate in scope with the claimed invention." The Patent Office also states that "in view of the lack of predictability of the art to which the invention pertains the lack of established protocols for effective adhesion-based therapies, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success..." (Office Action mailed May 13, 1997, paper number 44, paragraph 10).

The Patent Office suggests that 35 U.S.C. §112 requires an inventor to “teach how to effectively treat any disease or reach any therapeutic endpoint in humans...” or requires “development of effective in vivo human therapeutic methods” (Paper #44, page 3 upon which the rejection in paper #49 is biased, emphasis added). The Patent Office further, questions whether *in vitro* data which shows that soluble B7 and CD28 fusion proteins inhibit T cell proliferation when contacted to their target receptors is sufficient to enable one skilled in the art to practice the invention. Additionally, the Patent Office claims that undue experimentation is required to practice the invention. None of the Patent Office’s assertions are supported by the record.

**B. REJECTION OF CLAIMS 79-96 BASED UPON 35 U.S.C. §112, FIRST AND SECOND PARAGRAPHS**

The Patent Office rejects the pending claims under 35 U.S.C. §112, first and second paragraphs because the claimed invention is allegedly not described in a full, clear, concise and exact terms as to enable any person skilled in the art to make and use the invention. The Patent Office states that “[t]he instant claims are indefinite in the recitation of ‘B7’ and ‘containing amino acid residues from about position 1 to about position 215 of the amino acid sequence corresponding to the extracellular domain of B7 antigen ‘because their characteristics are ambiguous and not defined.... While the name itself may have some notion of the activity of the protein, there is nothing in the claims which distinctly claims the protein and variants thereof. Others in the field may isolate the same protein and give an entirely different name” (Office Action dated May 13, 1997, paper number 44, page 6)

Linsley et al.  
U.S. Serial No. 08/219,200  
Filed: March 29, 1994  
Page 6

The Patent Office further asserts that "the specification, while being enabled for a B7 protein as sequenced by Freedman et al... does not reasonably provide enablement for any B7 protein and, in turn, for any B7 fusion protein. The specification does not describe nor enable identification of any other B7 antigen meeting the structural or functional limitations of the instant invention and it is deemed to constitute undue experimentation to determine them" (paper number 44, page 6).

## **7. GROUPING OF THE CLAIMS**

Claims 79-94 are separately patentable from each other and the rejected claims do not stand or fall together because the claimed invention are methods directed separately to the use of two different molecules, namely, soluble CD28 and soluble B7 molecules. Using soluble CD28 is not the same as using soluble B7 and vice versa. Therefore, the rejected claims do not stand or fall together.

## **8. ARGUMENTS**

Applicants respectfully disagree with the Patent Office's rejection of the specification and the claims for the following reasons:

**A. REJECTION OF SPECIFICATION AND CLAIMS 79-96 UNDER 35 U.S.C.  
§112, FIRST PARAGRAPH**

**1. THE CLAIMED INVENTION IS ENABLED**

The Patent Office states that “[i]n vitro and animal model studies have not correlated well with in vivo clinical trial results in patents” (Paper #44 page 3), “[p]harmaceutical therapies in the absence of in vivo clinical data are unpredictable...” (Paper #44 page 3), and that the “specification does not adequately teach how to effectively treat any disease or reach any therapeutic endpoint in humans by B7 Ig or CD28 Ig fusion proteins” (Paper #44 page 4).

35 U.S.C. §112 requires that “the specification contain a written description of the invention, and ... enable any person skilled in the art to which it pertains, to make and use the same ...” (emphasis added). One is not required to enable any more than what is claimed. The Patent Office is improperly imposing a requirement that applicants demonstrate “commercial success” to meet the enablement requirement of 35 U.S.C. §112.

The methods of the invention as recited in amended claims 79 and 88 involve contacting soluble B7 or CD28 fusion protein to its respective receptor and thereby blocking the response of T or B cells to their normal endogenous ligand. The claims are not directed to methods of treating a patient. In determining whether or not the specification and the claims are enabled, the analysis must be directed to the claimed methods, which do not recite human therapy.

The specification sufficiently teaches one skilled in the art how to contact soluble B7 or CD28 protein to its respective target and thereby inhibit a T cell or B cell response. The present specification clearly teaches that administration of soluble B7 antigen results in binding to CD28 on T cells *in vitro*. These results are similar to those achieved by the use of anti-CD28 receptor antibodies *in vivo*. Thus, because anti-CD28 mAbs may exert either stimulatory or inhibitory effects on T cells *in vivo*, depending, in part, on the degrees of crosslinking or "aggregation" of the CD28 receptor (Damle, *J. Immunol.* 140:1753-1761 (1988); Ledbetter et al., *Blood* 75 (7):1531-1539 (1990)), it is expected that the B7 antigen, its fragments and derivatives, will act to stimulate or inhibit T cells in a manner similar to the effects observed for an anti-CD28 monoclonal antibody under similar conditions *in vivo* (specification at page 22, lines 1-9).

Concisely, administration of the CD28 antigen, or its fragments and derivatives *in vivo*, for example in the form of a soluble CD28Ig fusion protein, will result in binding of the soluble CD28Ig to B7 antigen on B7 positive T cells preventing endogenous stimulation of CD28 receptor by B7 positive cells such as activated B cells, and interfering with cell responses resulting from the interaction of B7 positive cells with T cells (specification at page 21, lines 26-32).

The Patent Office's requirement that Applicants "teach how to effectively treat any disease or reach any therapeutic endpoint in humans..." or teach the "development of effective *in vivo* human therapeutic methods" (Paper #44, page 3 upon which the rejection in paper #49 is based) to overcome the 35 U.S.C. §112 rejection is improper. All that is required, is to teach how to make and use the claimed invention. The specification teaches one skilled in the art to use the

invention in the claimed methods. The Patent Office's rejection of the specification and claims 79-94 should be reversed.

## 2. APPLICANTS *IN VITRO* DATA IS SUFFICIENT.

The Patent Office resurrects a previously argued and withdrawn argument that, because the invention is supported solely by *in vitro* data, it is not enabled. The Patent Office states that "[i]n vitro and animal studies have not correlated well with in vivo clinical trial results in patients" (paper #44, page 3). The Patent Office further states that

[p]harmaceutical therapies in the absence of in vivo clinical data are unpredictable for the following reasons: (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be absorbed by fluids, cells and tissue where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. (Office Action dated May 13, 1997, paper number 44, page 3)

The argument that the *in vitro* data provided in the specification does not enable the *in vivo* uses contemplated by the claims has had a long history in the file wrapper of this case. It was first brought up as a 35 U.S.C. § 101 rejection in the Office Action mailed March 25, 1992 (paper number 9, paragraph number 18), and also raised under 35 U.S.C. § 112 in that same paper (paragraph number 20). Applicants' provided the Patent Office with the reference Lenschow et al. (1992) (already of record) listing the Applicants as co-authors. Lenschow discloses *in vivo* data which show that blocking the CD28 receptor from binding the B7 antigen using only CD28 results in manipulating the immune system. Lenschow et al. conclude that blocking the interaction of co-stimulatory molecules such as CD28-B7 may provide a new approach to

immunosuppression. Based upon this successful argument the § 101 rejection was withdrawn in the next Office Action, (Office Action dated December 4, 1992, paper number 12, paragraph number 50), but the 35 U.S.C. § 112 argument was maintained, (paragraph number 21), and carried forward to the next Office Action (dated July 12, 1993, paper number 16, at paragraph number 20).

In the following Office Action, (dated August 17, 1994, paper number 29), the Patent Office, using new references, resurrects 35 U.S.C. §101 rejection for the pending claims for a second time, (paragraph 23), and rejects the specification under 35 U.S.C. § 112, (paragraph number 25), stating that the invention is inoperative and therefore lacks utility. The Patent Office states that “it is well known in the art that antibody-based therapies have very limited success. One of ordinary skill in the art would not readily accept that Applicants’ claimed modified antibodies would be satisfactory for human therapy as asserted in the specification.... Other factors such as proteolytic degradation, immunological inactivation, antigenic modulation or antigen shedding by the tumor, as well as factors influencing localization of the antibody such as the anatomical location of the tumor and its vascularity and blood flow, all have bearing on the efficacy of the antibody therapy.” (paper number 29, page 3) Again, in response to Applicants’ successful argument, the Patent Office withdrew the §101 rejection in the next Office Action, (dated April 26, 1995, paper number 30, paragraph number 21), but couches the rejection under 35 U.S.C. § 112, first paragraph, in the exact same language. The argument couched in utility terms is then repeated in the Office Action dated December 27, 1995 (paper number 36, paragraph number 20).

Withdrawing the §101 rejection but maintaining the §112 rejection, using arguments rooted in utility and operability, is improper. The rejection under section 112, first paragraph should be

Linsley et al.  
U.S. Serial No. 08/219,200  
Filed: March 29, 1994  
Page 11

withdrawn together with the correlative rejection under section 101<sup>1</sup>. Applicants have enabled and supported the utility of the claimed invention.

In response to the successful arguments by applicants, in the next Office Action dated September 13, 1996 (page number 39, paragraph number 21), the Patent Office dropped the argument that *in vitro* data does not enable the *in vivo* uses encompassed by the claims. The Examiner found that, based upon the *in vitro* data provided in the specification, B7 and CD28 Ig molecules **are enabled**. However, the Patent Office states that no other derivatives are enabled. (paper number 39, page 2, see quote below).

Then in the next Office Action dated May 13, 1997 (paper number 44, paragraph 10) the Patent Office reverses itself stating that upon “reconsideration … the instant claims drawn to inhibiting T cell response with soluble B7 and CD28 fusion proteins are considered **not enabled**” (emphasis added). The Patent Office resurrects the argument that due to the unpredictable nature of this art the *in vitro* data provided by applicants does not correlate well with *in vivo* clinical trial results and thus the claims are not enabled. The Patent Office repeats the exact language used in the 35 U.S.C. § 101 rejection, (paper number 29, paragraph 23 B), which had been withdrawn, and suggests that the *in vitro* data are unpredictable because the proteins may be inactivated, may not reach their target, or other unknown problems may arise in an *in vivo* setting.

In the Office Action dated September 13, 1996, the Patent Office stated that “… the specification, while being enabling for the use of B7Ig or CD28Ig in a method for inhibiting T cell proliferation,

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<sup>1</sup> Final PTO Utility Examination Guidelines (60 FR 36263).

does not reasonably provide enablement for the use of a generic B7/CD28 derivative or a method of inhibiting binding of B7 to CD28." (Paper number 39, page 2, underlining added for emphasis) The thrust of the Patent Office's argument in paper number 39 was that while B7Ig and CD28Ig derivatives were enabled by the specification, other molecules covered by the claims were not enabled. Now the Patent Office is reversing its position and arguing that B7 and CD28 Ig molecules are not enabled by the specification because "the specification did not provide direction or guidance as to a family of B7 molecules disclosed by Freeman et al" (paper 49, paragraph 8, page 4).

There should be a good faith effort on the part of the Patent Office to bring prosecution to a close and issue a patent where, as in the present case, applicants have earnestly sought to amend the claims and meet rejections, and where in fact applicants have fulfilled all requirements for patentability. The reversal of the previous positions the Patent Office has taken in this application, evidences a moving target approach to examination. When Applicants successfully argue against one rejection, the Patent Office reargues a prior argument or rejection that Applicants' have previously overcome. The Patent Office has been raising and withdrawing the same arguments dressed in different guises since 1991. This is contrary to the intent of the patent laws. The Patent Office must take a clear and consistent stance with regard to the patentability of Applicants' invention. This prosecution has been continuing for over seven years, having been prolonged by the Patent Office without justification.

Moreover, even if it were proper to maintain the rejection under section 112, first paragraph, despite the withdrawal of the corresponding rejection under section 101, the rejection under section 112, first paragraph, fails because, without more, the basis for the rejection is merely an

unsupported assertion. In this case, there is no basis for the Patent Office to assert that the claimed methods are not enabled by the data provided in the specification. The "problems" with using proteins *in vivo* as stated by the Patent Office (e.g., possible inactivation of the protein, questions of half life, ability of protein to reach its target, the protein's lack of ability to cross mucosa) are speculative and associated with the use of all compounds *in vivo* and are not particular to the use of the claimed proteins. These statements do not constitute a sufficiently definite statement of a basis for rejection<sup>2</sup>. The basis for the rejection is therefore not to the claimed invention and is improper and should be withdrawn. The Patent Office has not questioned whether Applicants have taught how to perform the claimed methods but only whether the claimed methods "will work."

The case law is clear, the Patent Office must treat as true Applicants' asserted use, unless the following exceptions exist:

1. the mode of operation of the claimed invention cannot be readily understood and does not conform to the known laws of physics and chemistry,
2. the mode of operation of the claimed invention operation conflicts with a recognized scientific principle as for example where an applicant purports to have discovered a machine producing perpetual motion, the presumption of inoperativeness is so strong that very clear evidence is required to overcome it,
3. the invention is of such a nature that it could not be tested by any known scientific principles<sup>3</sup>.

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<sup>2</sup> In re Chilowsky, 108 USPQ 321, 325 (1956).

<sup>3</sup> In re Brana et al., 34 USPQ2d 1438 (CAFC 1995).

Linsley et al.  
U.S. Serial No. 08/219,200  
Filed: March 29, 1994  
Page 14

In this regard, applicants point out that exception 1 above has not been met because the use of proteins, in general, and Ig fusion proteins, in particular, are well known and accepted (Applicants' response dated August 28, 1995, at pages 11-12).

Further, exception 2 above has not been met because the claimed methods are not limited to *in vivo* uses and they do not conflict with a recognized scientific principle. In fact, Applicants' *in vitro* data confirm the operability of the claimed methods because the data shows that the B7 ligand binds CD28 and the CD28 ligand binds B7 and that this binding produces the claimed result (specification at page 64, lines 21-25, lines 27-30; page 71, lines 5-9, lines 28-29, lines 29-35). Further, applicants provided *in vivo* data confirming the *in vitro* results using a homologous molecule, namely, CTLA4Ig (see Applicants' response dated August 24, 1992 of parent application, namely, U.S. Serial No. 722,101). This *in vivo* data strengthens Applicants' *in vitro* data.

Moreover, there is no reason to believe that the use of B7 and CD28 antigens would be unpredictable in view of the successful use of soluble homologous molecules, e.g., CTLA4, *in vivo*. In accordance with Brana, Applicants' *in vitro* evidence alone should be sufficient to satisfy Applicants' burden<sup>4</sup>. In combination with *in vivo* data concerning homologous molecules, there is no reason to doubt applicants' assertion.

Further the National Institute of Health (NIH) has approved several protocols involving the use of CD28. (see RAC Human Gene Therapy Protocols updated May 13, 1998, attached herewith

<sup>4</sup> In re Brana at page 1442.

as Exhibit 2, protocol numbers 9605-155, 9707-201, 9707-207, and 9709-215). To obtain NIH phase I approval one must provide data which sufficiently shows that the research you propose has a very substantial possibility of achieving the end result you desire. This is done generally through a showing of *in vitro* data which is predictive of the likely result in animal and human protocols. The fact that NIH has approved CD28 studies cuts against the Patent Office's argument that the art in this area is so unpredictable that *in vitro* data is not acceptable. The NIH approval for protocols using CD28 shows that *in vitro* data using B7 or CD28 has more than sufficient *in vivo* predictability.

The data provided by Applicants is sufficient to enable one skilled in the art to practice the invention as claimed. The Patent Office must adopt a clear and concise approach to the prosecution of this application and should withdraw the rejection under §112, first paragraph.

### **3. NO UNDUE EXPERIMENTATION IS REQUIRED TO OBTAIN B7 AND CD28 LIGANDS**

The Patent Office asserts that “[i]n view of the lack of predictability of the art to which the invention pertains the lack of established clinical protocols for effective adhesion-based therapies, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in the applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for inhibiting T cell function and interactions” (Paper number 44, paragraph number 10, page 5) The Patent Office maintains this argument in the latest Office Action, stating that “not only have immunoglobulin fusion proteins comprising B7 and CD28 have not met the claimed limitations

but neither have the various soluble proteins other than said immunoglobulins fusion proteins" (paper number 49, Paragraph number 6, page 2 typing in original).

The requirements of 35 U.S.C. §112, first paragraph are fulfilled where one skilled in the art could use the invention given the specification disclosure without undue experimentation<sup>3</sup>. Undue breadth is analyzed in terms of whether it would have involved undue experimentation to achieve the claimed invention. The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art<sup>4</sup>.

The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed<sup>5</sup>.

In *Ex parte Forman* the Board set forth the following criteria for undue experimentation:

The question of undue breadth is analyzed in the view of:

- (1) the quantity of experimentation necessary,
- (2) the amount of direction or guidance presented,
- (3) the presence or absence of working examples,

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<sup>3</sup> *In Re Eynde*, 480 F2d 1364, 178 USPQ 470 (CCPA 1970).

<sup>4</sup> *Ex parte Forman*, et al. 230 USPQ 546, 547 (BPAI 1986).

<sup>5</sup> *Ex parte Forman*, et al. 230 USPQ 546, 547 (BPAI 1986).

- (4) the nature of the invention,
- (5) the state of the prior art,
- (6) the relative skill of those in that art, and
- (7) the unpredictability of the art<sup>6</sup>.

The unpredictability of the art is only one factor that must be evaluated and weighed with the other factors. In the case of the present invention no undue experimentation would be required to make and use the invention as claimed. The claims are directed to contacting soluble B7 or CD28 ligand to its respective receptor. The amount of experimentation is minimal because applicants have conducted the relevant experiments which are disclosed in the present application. Ample guidance is presented by applicants as to how to make the B7 and CD28 fusion proteins and how to carry out the claimed methods. The nature of the invention is clear from the disclosure. The state of the prior art is such that making fusion proteins and introducing such proteins to contact cells and detecting responses of the cells or lack thereof could be carried out by one skilled in the art with Applicants' disclosure. The relative skill of the art is high, and use of fusion proteins to bind cell proteins is not unpredictable.

**B. REJECTION OF CLAIMS 79-96 BASED UPON 35 U.S.C. §112 FIRST AND SECOND PARAGRAPH**

In the Office Action dated December 10, 1997, the Patent Office asserts that the present claims are indefinite in the recitation of "B7" and "containing amino acid residues from about position 1 to about position 215 of the amino acid sequence corresponding to the extracellular domain of

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<sup>6</sup> Forman at page 547, *supra*.

B7 antigen" because their characteristics are allegedly ambiguous and not defined (paper number 49, page 4, and paper number 44, page 6). The Patent Office further asserts that while the specification is enabled for a B7 protein as sequenced by Freedman et al., it does not reasonably provide enablement for any B7 protein, and that the disclosure of a single B7 molecule does not provide enablement for any B7 protein (page 6).

The term "B7" is definite. Applicants have provided the entire nucleotide sequence for one B7 protein and described the functions which other members of the class of proteins provided by the invention would have to have. The specification's disclosure of B7's role as the ligand for CD28 or T cells defines the functional characteristic of this protein as claimed. In addition, B7 is the single art accepted term for this molecule as first described by Freedman et al., in "B7, A NEW MEMBER OF THE Ig SUPERFAMILY WITH UNIQUE EXPRESSION ON ACTIVATED AND NEOPLASTIC B CELLS" J. Immunol. 143: 2741-2722 (1989). Further art searches in this field (such as the one conducted by the Patent Office for paper #9) establish that "B7" is understood by those skilled in the art to be the protein having the characteristics of the protein as claimed.

35 U.S.C. § 112, first and second paragraph requires applicants to teach how to make and use the invention without undue experimentation. The law is clear. Applicants are not required to disclose every species encompassed by the claims (*In re Angstadt and Griffin*, 190 USPQ 215, 218 CCPA1976)). Moreover, despite the fact that applicants do not disclose every known B7 molecule, the identification of other species in the class would not entail undue experimentation because Applicants' disclosure outlines a number of different assays for the identification of B7 molecules as claimed. Practice of the claimed invention does not require undue experimentation.

Applicants' disclosure further teaches methods for regulating an immune response associated with T cell/ B cell interactions by specifically targeting the binding interactions of two well defined molecules, B7 and CD28 (see pages 19-29 of the application). The claimed methods are narrowly focused to recite regulation of T cell/B cell interactions through binding of these molecules and the disclosure of the present application provides examples of exemplary molecules as well as different assays which evaluate the utility of those molecules.

There is no undue experimentation involved in determining whether a B7 binding molecule will work in the claimed methods. Because the specification provides guidance for one having ordinary skill in the art on how to determine which species among the B7 molecules are among those encompassed by the claimed methods. The specification discloses complementary and redundant assays for B7 molecules encompassed by the claims, i.e. those molecules that effect cellular processes in their capacity to act as the ligand for the CD28 molecule on T cells.

For example, in the specification at page 43, the applicants disclose a protocol for a binding assay utilizing B7 and CD28 transfected COS cells to measure CD28 mediated adhesion. In this binding assay, the ability of COS transfected CD28 cells to bind COS cells transfected with a B7 molecule is evaluated. B7 construct and an anti-CD28 monoclonal antibody 9.3 here used as controls in these assays to specifically block this interaction. With those assays, any potential B7 molecule can be transfected into COS cells and tested for its ability to interact with CD28. As transfection constructs and antibody blocking assays are well known in the art, and the specification discloses representative constructs, these protocols are readily adapted for use in assays of a wide variety of molecules that have the potential to bind CD28.

Further, in the specification at page 61, applicants disclose a protocol for an ELISA assay tailored

to test B7, the ability of B7 molecules to bind CD28. This highly detailed description outlines the specific conditions for binding B7 molecules to immobilized CD28 molecules. As both B7 and CD28 constructs and ELISA protocols are well known in the art, the Applicants' illustrative binding protocols may be used to assay a wide variety of molecules that may bind CD28. In addition, the Applicants' disclosure of the B7Ig construct provides a competitor with known binding characteristics to use as a control in these assays.

In the specification at page 66, a protocol is described for measuring the effects of B7 binding on T cell proliferation. Specifically, a procedure for measuring T cell stimulation through CD28 is disclosed wherein T cell proliferation by B7 molecules is measured by uptake of [<sup>3</sup>H] for 5 hours. As a control in these assays, Applicants disclose both a B7 construct for use as a control in evaluating other members of this class. This tritium uptake protocol utilized by applicants is well known in the art and the Applicants' disclosure of such representative examples in the context of these proliferation protocols allows for ready adaptation of these protocols for use with a wide variety of B7 molecules that have the potential to activate T cells through the CD28 molecule on the surface of T cells.

In addition to the specific binding protocols discussed above, Applicants' disclosure of the specific B7 and CD28 constructs for use in such assays readily allows one skilled in the art to use other well known binding assays to evaluate a variety of molecules that may have the potential to bind CD28. In particular, the CD28 and B7 constructs and the disclosed antibodies to each, may be used in co-immunoprecipitation assays. In such assays, any molecule that binds to CD28 will be copurified in an immunoprecipitation reaction due to its affinity for the target molecule. Such co-immunoprecipitation assays are well known in the art and are a standard procedure for identifying whether a novel molecule binds to a defined target (see Dedhar et al., already of

record).

The disclosed representative molecules and example assays allow the skilled artisan to evaluate any novel B7 molecule for its ability to affect immune responses associated with B7 and CD28 binding interactions. In particular, any B7 molecule may be independently assayed via the multiple disclosed complementary tests for its ability to act as the ligand for CD28. In this way, the disclosure allows the skilled artisan, without undue experimentation, to determine which species among the claimed genus possesses the disclosed utility. This is all that is required by 35 U.S.C. §112.

Applicants meet the standard for objective enablement of any B7 protein. The specification discloses protocols and illustrative examples which one skilled in the art could use to readily determine other B7 protein encompassed by the invention

The Patent Office has not produced any reason for its assertion that other B7 proteins are not enabled on the claimed method. Therefore, B7 proteins are supported by the present application and the Patent Office's rejection should be withdrawn.

In view of the preceding remarks, applicants respectfully request that the Patent Office reconsider and withdraw the various grounds for objection and rejection set forth in the Office Action.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone her at the number provided below.

Linsley et al.  
U.S. Serial No. 08/219,200  
Filed: March 29, 1994  
Page 22

No fee, other than the fee for filing the Appeal brief, the extension fee and the fee for requesting oral argument is deemed necessary in connection with the filing of this Appeal Brief. If any fee is necessary, the Patent Office is authorized to charge any additional fee to Deposit Account No. 50-0306.

Respectfully submitted,

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## EXHIBIT 1

What is claimed is:

- 79. A method for inhibiting T cell proliferation resulting from binding of B7 and CD28 comprising contacting CD28 positive T cells with a soluble B7 fusion protein so as to bind CD28 on the CD28 positive T cells with the soluble B7 protein and thereby inhibiting T cell proliferation.
- 80. The method of claim 79, wherein the soluble B7 fusion protein has an amino acid sequence containing amino acid residues from about position 1 to about position 215 of the amino acid sequence corresponding to the extracellular domain of B7 which recognizes and binds the CD28 positive T cells.
- 81. The method of claim 79, wherein the soluble B7 fusion protein comprises a fusion polypeptide having a first amino acid sequence corresponding to the extracellular domain of B7 which recognizes and binds CD28 and a second amino acid sequence corresponding to a moiety that alters the solubility, affinity, and/or valency of the soluble B7 fusion protein for binding to CD28.
- 82. The method of claim 81, wherein the moiety is an immunoglobulin constant region.
- 83. The method of claim 82, wherein the immunoglobulin constant region is a human immunoglobulin Cy1 region.
- 84. The method of claim 79, wherein the soluble B7 fusion protein comprises a fusion polypeptide having a first amino acid sequence containing amino acid residues from about position 1 to about position 215 of the amino

acid sequence corresponding to the extracellular domain of the soluble B7 fusion protein which recognizes and binds CD28 and a second amino acid sequence corresponding to the hinge, CH2, and CH3 regions of human immunoglobulin C $\gamma$ 1.

- 85. A method for inhibiting the binding of CD28 positive T cells to B7 positive B cells comprising contacting the CD28 positive T cells with a soluble B7 fusion protein which recognizes and binds CD28 on the CD28 positive T cells thereby preventing binding of CD28 to B7 positive B cells.
- 86. The method of claim 85, wherein the soluble B7 fusion protein is a B7Ig fusion protein comprising an amino acid sequence containing amino acid residues from about position 1 to about position 215 of the amino acid sequence corresponding to the extracellular domain of B7 which recognizes and binds CD28.
- 87. The method of claim 86, wherein the fusion protein is B7Ig fusion protein having the amino acid sequence encoded by DNA contained in the plasmid having ATCC No. 68627.
- 88. A method of inhibiting CD28 positive T cell responses comprising reacting B7 positive B cells with a soluble CD28 fusion protein so as to bind the B7 positive B cells with the soluble CD28 fusion protein thereby inhibiting T cell responses caused by the binding of B7 and CD28.
- 89. The method of claim 88, wherein the soluble CD28 fusion protein comprises a polypeptide having an amino acid sequence containing amino acid residues from about position 1 to about position 134 of the amino acid sequence corresponding to the extracellular domain of CD28.

- 90. The method of claim 89, wherein the soluble CD28 fusion protein has a first amino acid sequence corresponding to the extracellular domain of CD28 and a second amino acid sequence corresponding to a moiety that alters the solubility, affinity, and/or valency of the CD28 for binding to B7 positive B cells.
- 91. The method of claim 90, wherein the moiety is an immunoglobulin constant region.
- 92. The method of claim 91, wherein the immunoglobulin constant region is a human immunoglobulin C $\gamma$ 1 region.
- 93. The method of claim 88, wherein the soluble CD28 fusion protein comprises a polypeptide having a first amino acid sequence containing amino acid residues from about position 1 to about position 134 of the amino acid sequence corresponding to the extracellular domain of CD28 and a second amino acid sequence corresponding to the hinge, CH2, and CH3 regions of human immunoglobulin C $\gamma$ 1.
- 94. The method of claim 93, wherein the fusion protein is CD28Ig fusion protein having the amino acid sequence encoded by DNA contained in the plasmid having ATCC No. 68628.

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- 80. The method of claim 79, wherein the soluble B7 fusion protein has an amino acid sequence containing amino acid residues from about position 1 to about position 215 of the amino acid sequence corresponding to the extracellular domain of B7 which recognizes and binds the CD28 positive T cells.
- 81. The method of claim 79, wherein the soluble B7 fusion protein comprises a fusion polypeptide having a first amino acid sequence corresponding to the extracellular domain of B7 which recognizes and binds CD28 and a second amino acid sequence corresponding to a moiety that alters the solubility, affinity, and/or valency of the soluble B7 fusion protein for binding to CD28.
- 82. The method of claim 81, wherein the moiety is an immunoglobulin constant region.
- 83. The method of claim 82, wherein the immunoglobulin constant region is a human immunoglobulin C $\gamma$ 1 region.
- 84. The method of claim 79, wherein the soluble B7 fusion protein comprises a fusion polypeptide having a first amino acid sequence containing amino acid residues from about position 1 to about position 215 of the amino

acid sequence corresponding to the extracellular domain of the soluble B7 fusion protein which recognizes and binds CD28 and a second amino acid sequence corresponding to the hinge, CH2, and CH3 regions of human immunoglobulin C $\gamma$ 1.

- 85. A method for inhibiting the binding of CD28 positive T cells to B7 positive B cells comprising contacting the CD28 positive T cells with a soluble B7 fusion protein which recognizes and binds CD28 on the CD28 positive T cells thereby preventing binding of CD28 to B7 positive B cells.
- 86. The method of claim 85, wherein the soluble B7 fusion protein is a B7Ig fusion protein comprising an amino acid sequence containing amino acid residues from about position 1 to about position 215 of the amino acid sequence corresponding to the extracellular domain of B7 which recognizes and binds CD28.
- 87. The method of claim 86, wherein the fusion protein is B7Ig fusion protein having the amino acid sequence encoded by DNA contained in the plasmid having ATCC No. 68627.
- 88. A method of inhibiting CD28 positive T cell responses comprising reacting B7 positive B cells with a soluble CD28 fusion protein so as to bind the B7 positive B cells with the soluble CD28 fusion protein thereby inhibiting T cell responses caused by the binding of B7 and CD28.
- 89. The method of claim 88, wherein the soluble CD28 fusion protein comprises a polypeptide having an amino acid sequence containing amino acid residues from about position 1 to about position 134 of the amino acid sequence corresponding to the extracellular domain of CD28.

- 90. The method of claim 89, wherein the soluble CD28 fusion protein has a first amino acid sequence corresponding to the extracellular domain of CD28 and a second amino acid sequence corresponding to a moiety that alters the solubility, affinity, and/or valency of the CD28 for binding to B7 positive B cells.
- 91. The method of claim 90, wherein the moiety is an immunoglobulin constant region.
- 92. The method of claim 91, wherein the immunoglobulin constant region is a human immunoglobulin C $\gamma$ 1 region.
- 93. The method of claim 88, wherein the soluble CD28 fusion protein comprises a polypeptide having a first amino acid sequence containing amino acid residues from about position 1 to about position 134 of the amino acid sequence corresponding to the extracellular domain of CD28 and a second amino acid sequence corresponding to the hinge, CH2, and CH3 regions of human immunoglobulin C $\gamma$ 1.
- 94. The method of claim 93, wherein the fusion protein is CD28Ig fusion protein having the amino acid sequence encoded by DNA contained in the plasmid having ATCC No. 68628.